Remarks

1. Status of the Claims

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 18-71 are pending in the application, with claims 18 and 38 being the independent claims. Claims 21, 24, 35-37, and 39-71 have been withdrawn further to the finality of the Examiner's restriction/election requirements. Claims 18, 28, 29, and 38 are sought to be amended. Support for the amendments to the claims can be found, *inter alia*, page 1, lines 5-10; page 8, lines 10-18; page 13, line 22 to page 14, line 3; page 14, lines 4-20; page 15, lines 2-22; page 16, lines 14-25; page 22, lines 4-22; Example 2 (pages 43-46); and the Abstract of the application as filed. These changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding rejections and that they be withdrawn.

2. Priority

In the Office Action dated November 16, 2009 ("Office Action"), the Examiner has indicated that priority documents submitted under 35 U.S.C. § 119(a)-(d) have been acknowledged and placed of record. Office Action, page 4.

The Examiner further indicates that translations for KR 10-2004-0003610 and KR 10-2004-0003957 were not provided, and that "applicants may not receive full

benefit of the foreign priority documents. See 37 CFR 1.55 and MPEP § 201.15."

Office Action, page 4.

Applicants note that under 37 C.F.R. 1.55(a)(4):

> (i) An English language translation of a non-English language foreign application is not required except:
>
> (A) When the application is involved in an interference (see § 41.202 of this title),
>
> (B) When necessary to overcome the date of a reference relied upon by the examiner, or
>
> (C) When specifically required by the examiner.
>
> (ii) If an English language translation is required, it must be filed together with a statement that the translation of the certified copy is accurate.

The Examiner has not indicated that any of the exceptions in 37 C.F.R. 1.55(a)(4)(i)(A)-(C) apply to the current application. Thus, it is not believed that an English language translation is required to receive the full benefit of the foreign priority documents. However, Applicants submit herewith English translations of for KR 10-2004-0003610 (with Declaration) and KR 10-2004-0003957 (with Declaration) as Appendix A and B, respectively. The Declarations provided with the English translations each include a statement from Lee Ah-Rah, translator for the documents, indicating that the translation is true and correct to the best of his knowledge. Applicants respectfully request that these documents be acknowledged and made of record.

3. Summary of the Office Action

In the Office Action, the Examiner made three rejections to the claims, and one provisional nonstatutory obvious-type double patenting rejection. Applicants respectfully offer the following remarks concerning the rejections.

4. Rejection under 35 U.S.C. § 112

At pages 4-5 of the Office Action, the Examiner has rejected claims 18-20, 22, 23, 25-34, and 38 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter applicants regard as the invention. In particular, the Examiner questioned, for example: is the polynucleotide encoding a target protein of method step (a) the same as (at least one of) the polynucleotide fragments of method step (b). What is the TFP comprised of? Is the TFP a fusion of target protein and reporter protein? Does the TFP include anything that the polynucleotide fragments encode? What is the purpose of the polynucleotide fragments if they are not analyzed for in the method?

Applicants respectfully traverse this rejection. However, in an effort to advance prosecution, Applicants have amended claims 18 and 38 in an attempt to make the claims more clear, and provide the following comments.

Is the polynucleotide encoding a target protein of method step (a) the same as (at least one of) the polynucleotide fragments of method step (b)?

First, the plurality of polynucleotide fragments of (b) are distinct from the polynucleotide encoding a target protein of (a). The present invention is directed to a method identifying a translational fusion partner (TFP) capable of stimulating the secretion of a target protein, which is poorly secreted in recombinant production. The methods of the claimed invention include the preparation of an automatic screening vector comprising a fusion polynucleotide encoding a fusion polypeptide comprising said target protein (X) linked to a reporter protein (R). The plurality of polynucleotide

fragments of (b) include TFP candidates, which are linked to the automatic screening vector (comprising X and R) to create a library.

What is the TFP comprised of?

The specification includes extensive disclosure related to TFP. For example, page 14, lines 21-26 of the specification, discloses that TFP can refer to a gene that is fused to a gene encoding a non-producible protein and induces the secretory production of the non-producible protein. Furthermore, TFP can be from, *e.g.*, genomic DNA or cDNA, and may be obtained from a variety of origins, *e.g.*, animals, plants and microorganisms, including yeasts or humans (see page 16, lines 3-13 of the specification).

Is the TFP a fusion of target protein and reporter protein?

As discussed above, the plurality of polynucleotide fragments include TFP candidates that can be linked to the automatic screening vector (comprising a target protein and a reporter protein) to create a library.

Does the TFP include anything that the polynucleotide fragments encode?

One or more of said plurality of polynucleotide fragments comprises TFP which is capable of inducing secretion of said fusion polypeptide.

What is the purpose of the polynucleotide fragments if they are not analyzed for in the method?

The plurality of polynucleotide fragments, which include candidate TFPs, are linked to the automated screening vectors to create a library. The library is screened for TFPs that are capable of stimulating secretion of a target protein, which is poorly secreted by conventional recombinant production methods.

It is believed that the remarks above address all of the Examiner's questions and that the claims as amended are clear. Thus, it is respectfully requested that the Examiner reconsider and withdraw the 35 U.S.C. § 112 rejection.

5. Rejection under 35 U.S.C. § 102

At pages 5-6 of the Office Action, the Examiner has rejected claims 18, 19, 23, 25, 28-33, and 38 as allegedly being anticipated under 35 U.S.C. § 102(b) by U.S. Patent No. 6,136,569, Baker et al. (hereafter '569) and PCT Publ. No. WO99/49028, Baker et al. (hereafter WO99/49028). Applicants respectfully traverse this rejection.

'569 and WO99/49028 relate to methods of identifying cDNAs, which encode secreted and membrane-bound proteins by detecting their signal sequences using a reporter system. *See* '569, *e.g.*, at col. 2, lines 46-57 and the Abstract; and WO99/49028, *e.g.*, at page 2, lines 28-30 and the Abstract. The methods of '569 and WO99/49028 disclose vectors prepared by fusing an amylase gene lacking a functional signal sequence with cDNA libraries containing signal sequences. *See* '569 at col. 9, lines 7-35 and WO99/49028 at page 9, lines 34-36. However, '569 and WO99/49028 fail to disclose part (a) of the current invention as presently claimed. In particular, '569 and WO99/49028 do not disclose preparing an automatic screening vector comprising a polynucleotide encoding a fusion polypeptide that comprises a target protein—which is poorly secreted by recombinant production—linked to a reporter protein.

An important distinguishing feature of the present invention is part (a) of claims 18 and 38. The current invention includes the preparation of an automatic screen vector in which a reporter gene is linked to a gene sequence encoding the poorly secreted target

protein, such that secretion of the reporter protein from host cells is inhibited by fusion to the poorly-secreted target protein. For example, this effect is disclosed on page 16, line 14-23 of the specification, which explains that when a poorly secreted target protein is fused to a reporter protein, such as invertase, the secretion of the reporter protein from host cells is significantly inhibited. Furthermore, a working example of (a) is disclosed in Example 2 (pages 43-46), which demonstrates that the expression of invertase was poor when fused to IL-2 (an example of a poorly-secreted target protein).

In contrast, when cDNA containing a signal sequence was fused to amylase in '569 and WO99/49028, amylase was efficiently secreted. That is, fusion of the cDNA of '569 and WO99/49028 to a reporter protein does not inhibit secretion of the reporter protein when fused thereto. Therefore, '569 and WO99/49028 do not disclose preparing an automatic screening vector comprising a polynucleotide encoding a poorly secreted target protein linked to a reporter protein as specified in (a) of amended claims 18 and 38.

Furthermore, the results achieved by the claimed invention differ from those disclosed in documents '569 and WO99/49028. In particular, secretion of the protein encoded by the reporter gene is inhibited by fusion to the poorly-secreted target protein, and thus, the present invention provides a method capable of rapidly screening for a suitable translational fusion partner (TFP) *capable of inducing secretion of a poorly-secreted target protein linked to a reporter protein*. In contrast, the methods of '569 and WO99/49028 allow for the identification of signal sequences *capable inducing the secretion of a reporter protein*.

As discussed above neither '569 or WO99/49028 teach every limitation of claims 18 and 38 and furthermore these cited references cannot anticipate claims 19, 23, 25, and 28-33, which depend therefrom. Therefore, it is respectfully requested that the rejection of claims 18, 19, 23, 25, 28-33, and 38 under 35 U.S.C. § 102(b) as being anticipated by '569 and WO99/49028 be reconsidered and withdrawn.

6. Rejection under 35 U.S.C. § 103

At pages 6-8 of the Office Action, the Examiner has rejected claims 18-20, 22, 23, 25-34, and 38 under 35 U.S.C. § 103(a) as allegedly being obvious over '569, U.S. Patent 5,212,058, Baker et al. (hereafter '058), and U.S. Patent 5,547,871, Black et al. (hereafter '871). Applicants respectfully traverse this rejection.

In particular, the Examiner asserts that it would have been obvious because the substitution of one known element (i.e. genus of genomic DNA library, genus of promoter, and genus of secretion signals or fusion proteins as taught by Baker et al.) for another (i.e. species of yeast gDNA library and species of Gal10 promoter taught by Baker et al. and species of human IL-2 taught by Black et al.) would have yielded predictable results (i.e. screening for secreted yeast polypeptides encoded by yeast gDNA, polypeptide expression in yeast via Gal10 promoter in vectors, and secretion) to one of ordinary skill in the art at the time of the invention. Office Action, pages 7-8. Applicants respectfully disagree.

The disclosure of '058 relates to a generic class of ubiquitin-specific proteases which specifically cleave at the C-terminus of the ubiquitin moiety in a ubiquitin fusion protein, and '871 relates to identification of heterologous signal sequences which

facilitate the expression and secretion of insect controlling proteins. The combination of '569, '058, and '871 does not predict all of the elements of the claimed invention. As discussed above, '569 fails to disclose a TFP screening method that includes preparing an automatic screening vector comprising a polynucleotide encoding a fusion polypeptide that comprises a poorly secreted target protein linked to a reporter protein as specified in (a) of amended claims 18 and 38. Neither '058 or '871 cure this deficiency. Thus, the documents cited by the Examiner cannot alone or in combination render the claimed invention obvious.

At pages 8-9 of the Office Action, the Examiner has rejected claims 18-20, 22, 23, 25-34, and 38 as allegedly being obvious under 35 U.S.C. § 103 in view of WO 99/49028, '058, and U.S. Patent 5,712,113 ('113). Applicants respectfully traverse this rejection.

In particular, the Examiner asserts that it would have been obvious because the substitution of one known element (i.e. genus of genomic DNA library, genus of promoter, and genus of secretion signals or fusion proteins as taught by Baker et al.) for another (i.e. species of yeast gDNA library and species of Gal10 promoter taught by Baker et al. and species of human IL-2 and species of Gal10 promoter taught by Chung et al.) would have yielded predictable results (i.e. screening for secreted yeast polypeptides encoded by yeast gDNA, polypeptide expression in yeast via Gal10 promoter in vectors, and secretion) to one of ordinary skill in the art at the time of the invention. Office Action, pages 8-9. Applicants respectfully disagree.

The disclosures of WO 99/49028 and '058 are discussed above. '113 discloses secretion signal peptides of inulinase enzymes which cause heterologous proteins produced in yeast cells to be secreted almost completely out of the cell. Applicants respectfully point out that '113 does not disclose a screening method at all.

Thus, WO 99/49028, '058 and '113 fail to disclose a TFP screening method that includes preparing an automatic screening vector comprising a polynucleotide encoding a fusion polypeptide that comprises a poorly secreted target protein linked to a reporter protein as specified in (a) of amended claims 18 and 38. The combination of '058 and '113 does not predict all of the elements of the claimed invention. Thus, the documents cited by the Examiner cannot alone or in combination render the claimed invention obvious.

Because the cited references do not teach all of the limitations of the claims as amended, the claims are not rendered obvious and Applicants respectfully request that the rejection under 35 U.S.C. § 103 be reconsidered and withdrawn.

7. Provisional Obviousness-Type Double Patenting Rejection

At pages 9-10 of the Office Action, the Examiner has provisionally rejected claims 18-20, 22, 23, 25-34, and 38 as allegedly being unpatentable over claims 1-4, 11-17, 21-25, 33-35, 39-42, 45-47, 50-51, 54-55, 72, 74, 76-80, 86, 91, 97, 100, 105, 109, 114, 117, and 119 of U.S. Appl. No. 11/914,437 ("'437"). In particular, the Examiner indicates that although the claims are not identical, they are allegedly not distinct from each other because both the presently claimed methods and the methods as claimed in '437 are drawn to methods of identifying TFP.

Applicants respectfully traverse this provisional rejection for nonstatutory obviousness-type double patenting, but nevertheless request that it be held in abeyance until the remaining issues outstanding in this application have been resolved.

In addition, Applicants note that the '437 application is a National Stage Entry of PCT/IB2006/003102 filed on July 13, 2006, while the present application (10/586,045) is a National Stage Entry of PCT/KR04/03517 filed on December 30, 2004. According to the M.P.E.P:

> If a "provisional" nonstatutory obviousness-type double patenting (ODP) rejection is the only rejection remaining in the earlier filed of the two pending applications, while the later-filed application is rejectable on other grounds, the examiner should withdraw that rejection and permit the earlier-filed application to issue as a patent without a terminal disclaimer.

M.P.E.P. § 804.I.B.1

Thus, if the nonstatutory obviousness-type double patenting rejection over the '437 application is the only rejection remaining in the above-captioned application (*i.e.*, the "earlier filed of the two pending applications"), the double patenting rejection should be withdrawn without the need for a terminal disclaimer.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will

expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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